L Number	Hits	Search Text	DB	Time stamp
-	1	"4788219" .pn.	USPAT; US-PGPUB	2003/06/01 23:42
-	1	"5057304" .pn.	USPAT; US-PGPUB	2003/06/01 23:44
-	3142	verapamil	USPAT; US-PGPUB	2003/06/01 23:44
-	4672	glucuronidase	USPAT; US-PGPUB	2003/06/01 23:45
-	62	verapamil and glucuronidase	USPAT; US-PGPUB	2003/06/01 23:46

{ Glucosidaronase UidA
dihydropyridine analogue
p-glycoprotein }

```
     FILE 'BIOSIS, CAPLUS, EMBASE, USPATFULL, JAPIO, TOXCENTER' ENTERED AT
     10:30:28 ON 02 JUN 2003
L2        87273 S 52-53-9/RN OR 460325-60-4/RN OR 460325-59-1/RN OR 302825-79-2

     FILE 'CAPLUS' ENTERED AT 10:33:44 ON 02 JUN 2003
                E GLUCURONIDASE/CT
                E E3+ALL
                E GLUCURONIDASE/CT
L3         8639 S E3,E4,E5,E6
L4          736 S .BETA.-GLUCORONIDASE OR GLUCURONIDASE, .BETA.
L5         8788 S L3 OR L4

     FILE 'BIOSIS, CAPLUS, EMBASE, USPATFULL, JAPIO, TOXCENTER' ENTERED AT
     10:36:06 ON 02 JUN 2003
L6        12816 S L5
L7           14 S L6 AND L2
L8           12 DUP REM L7 (2 DUPLICATES REMOVED)
                SET SMA OFF
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     FILE 'CAPLUS' ENTERED AT 10:39:26 ON 02 JUN 2003
L10           1 S L***

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     10:39:29 ON 02 JUN 2003
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                SET SMA LOGIN

     FILE 'CAPLUS' ENTERED AT 10:40:13 ON 02 JUN 2003
L12           1 S L***

     FILE 'BIOSIS, CAPLUS, EMBASE, USPATFULL, JAPIO, TOXCENTER' ENTERED AT
     10:40:16 ON 02 JUN 2003
                SET SMA OFF
                SET SMA ON
                SET SMA LOGIN

     FILE 'CAPLUS' ENTERED AT 10:40:46 ON 02 JUN 2003
L14           1 S L***

     FILE 'BIOSIS, CAPLUS, EMBASE, USPATFULL, JAPIO, TOXCENTER' ENTERED AT
     10:40:49 ON 02 JUN 2003
                SET SMA OFF
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                SET SMA LOGIN

     FILE 'CAPLUS' ENTERED AT 10:41:13 ON 02 JUN 2003
L16           1 S L***

     FILE 'BIOSIS, CAPLUS, EMBASE, USPATFULL, JAPIO, TOXCENTER' ENTERED AT
     10:41:16 ON 02 JUN 2003
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2

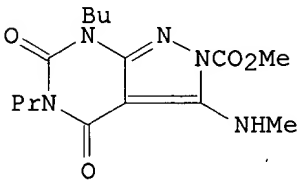
ACCESSION NUMBER: 1986:96516 BIOSIS
DOCUMENT NUMBER: BA81:6932
TITLE: DIPHENYLHYDANTOIN INHIBITS PARATHYROID HORMONE AND PROSTAGLANDIN E-2-STIMULATED BONE RESORPTION IN MOUSE CALVARIA WITHOUT AFFECTING CYCLIC AMP FORMATION.
AUTHOR(S): LERNER U; FREDHOLM B B; HANSTROM L
CORPORATE SOURCE: DEPARTMENT ORAL PATHOLOGY, UNIVERSITY UMEA, S-901 87 UMEA, SWEDEN.
SOURCE: J ORAL PATHOL, (1985) 14 (8), 644-653.
CODEN: JOPHBO. ISSN: 0300-9777.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The effect of diphenylhydantoin (DPH) on mouse calvarial bone metabolism was studied in vitro. DPH caused a dose-dependent, reversible inhibition of PTH and PGE2-stimulated bone resorption at concentrations above 20-30 .mu.g/ml without affecting cyclic AMP formation. The inhibition was observed already after 60 min and was accompanied by a reduced release of the lysosomal enzymes .beta.-glucuronidase and .beta.-N-acetylglucosaminidase. The calcium antagonist **Verapamil** had similar effects on bone resorption and lysosomal enzyme release and it is suggested that DPH influences bone resorption by interfering with calcium fluxes across osteoclastic cell membranes resulting in low intracellular calcium levels and reduced exocytotic processes.

IT Miscellaneous Descriptors
VERAPAMIL BETA **GLUCURONIDASE BETA**-N ACETYLGLUCOSAMINIDASE

RN 52-53-9 (**VERAPAMIL**)
57-41-0 (DIPHENYLHYDANTOIN)
60-92-4 (CYCLIC AMP)
363-24-6 (PROSTAGLANDIN E-2)
9001-45-0 (BETA GLUCURONIDASE)
9012-33-3 (BETA-N ACETYLGLUCOSAMINIDASE)

L8 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:608842 CAPLUS
DOCUMENT NUMBER: 111:208842
TITLE: Inhibitory effects of methyl 7-butyl-4,5,6,7-tetrahydro-3-methylamino-4,6-dioxo-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-2-carboxylate (AA-2379) on lysozomal enzyme and arachidonic acid release from rat polymorphonuclear leukocytes and its mode of action
AUTHOR(S): Makino, H.; Saijo, T.; Maki, Y.
CORPORATE SOURCE: Cent. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan
SOURCE: Agents and Actions (1989), 28(3-4), 248-55
CODEN: AGACBH; ISSN: 0065-4299
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The effect of AA-2379 (I) on rat polymorphonulear leukocyte (PMN) functions was studied to clarify the mechanism of the antiinflammatory and antiallergic actions of AA-2379. AA-2379 at 10-4 inhibited lysozomal enzyme release. AA-2379 inhibited formyl methionyl-leucyl-phenylalanine (fMLP)- and C5a-induced acid release; their 50% inhibitory concns. were 2.8 .times. 10-5 and 3.8 .times. 10-5 M, resp. Because dibutyryl cAMP, a cAMP analog, and 3-isobutyl-1-methylxanthine, a cAMP phosphodiesterase inhibitor, inhibited fMLP-induced arachidonic acid release, and AA-2379 inhibited cAMP phosphodiesterase and increased cAMP content in PMNs, it is likely that AA-2379 inhibited arachidonic acid release by increasing cAMP content in rat PMNs. Furthermore, from the studies of fMLP-induced arachidonic acid release in Ca free medium, it is suggested that AA-2379 inhibits the process which depends on Ca concn. in the medium. Thus, the inhibitory effect of AA-2379 on inflammation and allergic reactions such as the Arthus reaction is partly exerted by inhibiting PMN functions such as arachidonic acid and lysozomal enzyme release.

IT Arthus phenomenon
(AA 2379 effect on)

IT Allergy
Inflammation
(AA 2379 inhibition of, mechanism of)

IT Leukocyte
(polymorphonuclear, function of, AA 2379 effect on)

IT 60-92-4, CAMP 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(AA 2379 inhibition of arachidonic acid release from leukocyte in relation to)

IT 103446-98-6, AA 2379
RL: BIOL (Biological study)
(arachidonic acid and lysozomal enzyme release response to, from leukocytes, antiallergic and antiinflammatory mechanism in relation to)

IT **52-53-9, Verapamil** 83-89-6, Quinacrine 99-73-0, 4-Bromophenacyl bromide 117-89-5, Trifluoperazine 28822-58-4

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(arachidonic acid release from leukocyte response to)

IT **9001-45-0**, .beta.-Glucuronidase 9001-63-2, Lysozyme
RL: BIOL (Biological study)
(inhibition of lysozomal release of, by AA 2379)

IT 9036-21-9, CAMP phosphodiesterase
RL: BIOL (Biological study)
(of lung, AA 2379 effect on)

8 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:880953 CAPLUS
DOCUMENT NUMBER: 134:37057
TITLE: Use of **verapamil** and **verapamil** derivatives for producing medicaments inhibiting .beta.-glucuronidase in human tissue
INVENTOR(S): Geisslinger, Gerd; Kroemer, Heyo K.; Sperker, Bernhard
PATENT ASSIGNEE(S): Paz Arzneimittel-Entwicklungs G.m.b.H., Germany
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000074670	A1	20001214	WO 2000-EP4848	20000527
W: CA, JP, RU, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19925810	A1	20001214	DE 1999-19925810	19990607
EP 1183023	A1	20020306	EP 2000-931265	20000527
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003501384	T2	20030114	JP 2001-501207	20000527

PRIORITY APPLN. INFO.: DE 1999-19925810 A 19990607
WO 2000-EP4848 W 20000527

AB **Verapamil** and **verapamil** derivs. are used for producing medicaments which inhibit .beta.-glucuronidase in human tissue.

IT Animal cell line
(Hep G2; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Detoxification
(biol.; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Antibodies
Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates, with .beta.-glucuronidase; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Drug delivery systems
(controlled-release, and std.-release; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Glycosides
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glucuronides, conjugates; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Drug delivery systems
(liposomes; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Antitumor agents
(metastasis; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Drug delivery systems
(oral; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Drug delivery systems
(parenterals; **verapamil** and **verapamil** derivs. for

.beta.-glucuronidase inhibitors)

IT Drug delivery systems
(prodrugs, glucuronide; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Antitumor agents
Digestive tract
Enantiomers
(**verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Drug metabolism
(**verapamil** metabolites; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT Escherichia coli
Liver
(.beta.-glucuronidase; **verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT 389-36-6, D-Glucaric acid, 1,4-lactone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT **52-53-9**, **Verapamil** 52-53-9D, **Verapamil**, derivs. **9001-45-0D**, .beta.-Glucuronidase, conjugates
16662-47-8, Gallopamil 16662-47-8D, Gallopamil, metabolites
34245-14-2, D-617 **38176-10-2** 38176-10-2D, metabolites
38321-02-7 38321-02-7D, derivs. 67018-80-8, D-703
67018-85-3, Norverapamil 77326-93-3, D-702
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT 57-27-2, Morphine, biological studies 6160-80-1, 4-Methylumbelliferyl-.beta.-D-glucuronide **9001-45-0**, .beta.-Glucuronidase
20290-09-9, Morphine-3-glucuronide 20290-10-2, Morphine-6-glucuronide
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

IT 90-33-5, 4-Methylumbelliferone
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(**verapamil** and **verapamil** derivs. for .beta.-glucuronidase inhibitors)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:340734 CAPLUS
DOCUMENT NUMBER: 138:49335
TITLE: **Verapamil** decreases glucuronidase activity in the gut
AUTHOR(S): Lotsch, Jorn; Sperker, Bernhard; Kroemer, Heyo K.; Geisslinger, Gerd
CORPORATE SOURCE: Department of Clinical Pharmacology, Pharmazentrum Frankfurt, Johann Wolfgang Goethe-University Hospital, Frankfurt, D-60590, Germany
SOURCE: Biochemical Pharmacology (2002), 63(8), 1575-1578
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present investigation addressed the role of **verapamil** for oral pharmacokinetics of morphine-6-.beta.-glucuronide (M6G). Male Sprague-Dawley rats received 62.5 mg kg-1 M6G-dihydrate orally w/wo pre-treatment with 70 mg kg-1 **verapamil**. I.v. M6G (3.9 mg kg-1) and oral morphine (52.7 mg kg-1 morphine-hydrochloride) were also employed. Oral bioavailability of M6G and the fraction of M6G deglucuronidated to morphine were estd. from areas under the plasma-concn. vs. time curves (AUC) of morphine and its glucuronides. As initial results pointed towards inhibition of glucuronidases by **verapamil**, its capability to specifically inhibit E. coli and/or rat intestinal .beta.-glucuronidase was assessed using altered cleavage of the model substrate 4-methylumbelliferyl-.beta.-d-glucuronide (MUG). Oral bioavailability of M6G was 2.1%; 13% of oral M6G was deglucuronidated to morphine. Co-administration of **verapamil** did not increase the AUC of M6G. AUCs of morphine and morphine-3-glucuronide were smaller in the **verapamil** group than in controls. **Verapamil** co-administration decreased the fraction of M6G deglucuronidated to morphine to 4.6%. In vitro expts. provided evidence that **verapamil** inhibits .beta.-glucuronidase from E. coli with an ic50 of 30 .mu.M, whereas no inhibition of the rat .beta.-glucuronidase from small intestine was seen. In conclusion, **verapamil** decreased intestinal deglucuronidation of M6G by inhibiting E. coli .beta.-glucuronidase. This indicates that **verapamil** is not suited as P-gp inhibitor in expts. involving glucuronides. An increase in the intestinal absorption of M6G due to P-gp-inhibition was not obsd. at the **verapamil** dose studied.
IT Drug delivery systems
(injections, i.v.; **verapamil** decreases glucuronidase activity in gut)
IT Drug delivery systems
(oral; **verapamil** decreases glucuronidase activity in gut)
IT Drug interactions
(pharmacokinetic; **verapamil** decreases glucuronidase activity in gut)
IT Intestine
(small; **verapamil** decreases glucuronidase activity in gut)
IT Drug bioavailability
(**verapamil** decreases glucuronidase activity in gut)
IT **9001-45-0**, .beta.-Glucuronidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**verapamil** decreases glucuronidase activity in gut)
IT **52-53-9**, **Verapamil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**verapamil** decreases glucuronidase activity in gut)
IT 57-27-2, Morphine, biological studies 20290-09-9, Morphine-3-glucuronide 20290-10-2, Morphine-6-glucuronide

RL: PKT (Pharmacokinetics); BIOL (Biological study)
(**verapamil** decreases glucuronidase activity in gut)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN **1995:315547** CAPLUS
DN 122:188019
TI Preparation of substrate-spacer-active substance prodrugs
IN Bosslet, Klaus; Czech, Joerg; Hoffmann, Dieter; Kolar, Cenek; Tillequin, Francois; Florent, Jean Claude; Azoulay, Michel; Monneret, Claude; Jacquesy, Jean Claude; et al.
PA Behringwerke AG, Germany
SO Ger. Offen., 17 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 4236237	A1	19940428	DE 1992-4236237	19921027
	EP 647450	A1	19950412	EP 1993-114475	19930909
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	EP 595133	A2	19940504	EP 1993-116702	19931015
	EP 595133	A3	19981104		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	IL 107398	A1	20010128	IL 1993-107398	19931025
	CA 2109259	AA	19940428	CA 1993-2109259	19931026
	NO 9303854	A	19940428	NO 1993-3854	19931026
	AU 9350225	A1	19940512	AU 1993-50225	19931026
	AU 669218	B2	19960530		
	JP 06293665	A2	19941021	JP 1993-266976	19931026
	ZA 9307951	A	19950705	ZA 1993-7951	19931026
	US 5955100	A	19990921	US 1995-449021	19950524
	US 6146658	A	20001114	US 1997-859084	19970520
PRAI	DE 1992-4236237		19921027		
	US 1993-140825	A3	19931025		
	US 1995-449021	A1	19950524		

AB Compds. of the form substrate-spacer-active substance, where the substrate and spacer are cleaved under physiol. or pathophysiol. conditions, the substrate is not an amino acid or peptide residue, and the active ingredient is a chem. compd. with biol. activity or a deriv. thereof, with the exception of N-bonded derivs. of anthracycline, paranitroanilide, or cytosine arabinoside, were prepd. Thus, 3'-N-fluorenylmethoxycarbonyldoxorubicin in PhMe was treated with diisopropylethylamine and diphosgene; after 1 h 4-(6-O-methyl-.beta.-D-glucuronyloxy)-3-nitrobenzylamine and diisopropylethylamine in DMF were added and the mixt. was stirred 14 h to give, after deprotection, 14-O-[4-(.beta.-D-glucuronyloxy)-3-nitrobenzylaminocarbonyl]doxorubicin (I). I showed an acute LD50 in mice of >1500 mg/kg, vs. 20 mg/kg for doxorubicin itself. I at 500 mg/kg in mice implanted with human LOVO colon tumors showed a T/C = 40.0%.

L12 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN **1998:189810** CAPLUS
DN 128:312812
TI Elucidation of the mechanism enabling tumor selective prodrug monotherapy
AU Bosslet, Klaus; Straub, Rainer; Blumrich, Matthias; Czech, Joerg; Gerken, Manfred; Sperker, Bernhard; Kroemer, Heyo K.; Gesson, Jean-Pierre; Koch, Michel; Monneret, Claude
CS Hoechst Research Laboratories, c/o Behringwerke AG, Marburg, 35001, Germany
SO Cancer Research (1998), 58(6), 1195-1201
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Elucidation of the mechanism enabling tumor selective prodrug monotherapy (PMT) in vivo with appropriate glucuronyl-spacer-doxorubicin prodrugs, such as HMR 1826, is important for the design of clin. studies, as well as for the development of more selective drugs. Enzyme histochem., immunohistochem., and the terminal deoxytransferase technique were applied using human cryopreserved cancer tissues, normal human, monkey, and mouse tissues, and human tumor xenografts to examine mechanisms underlying the selectivity of successful PMT with HMR 1826. It could unambiguously be shown by enzyme histochem. that necrotic areas in human cancers are the sites in which lysosomal .beta.-glucuronidase is liberated extracellularly in high local concns. The cells responsible for the liberation of the enzyme are mainly acute and chronic inflammatory cells, as shown by IHC. Furthermore, it could be demonstrated that .beta.-glucuronidase liberated in necrotic areas of tumors can activate HMR 1826, resulting in increased doxorubicin deposition in human tumor xenografts or in human lung cancers subjected to extracorporeal perfusion, compared to chemotherapy with doxorubicin. Addnl., the doxorubicin load to normal tissues was significantly reduced compared to chemotherapy with doxorubicin. Surprisingly, the increased doxorubicin deposition in tumors also resulted in strong antitumor effects also in cancers resistant to max. tolerated doses of systemic doxorubicin. Finally, toxicity studies in mice and monkeys revealed an excellent tolerability of HMR 1826, up to a dose of 3 g/m2 (monkeys). These data suggest that HMR 1826 is a promising candidate for clin. development.
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN **1998:189810** CAPLUS
DN 128:312812
TI Elucidation of the mechanism enabling tumor selective prodrug monotherapy
AU Bosslet, Klaus; Straub, Rainer; Blumrich, Matthias; Czech, Joerg; Gerken, Manfred; Sperker, Bernhard; Kroemer, Heyo K.; Gesson, Jean-Pierre; Koch, Michel; Monneret, Claude
CS Hoechst Research Laboratories, c/o Behringwerke AG, Marburg, 35001, Germany
SO Cancer Research (1998), 58(6), 1195-1201
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Elucidation of the mechanism enabling tumor selective prodrug monotherapy (PMT) in vivo with appropriate glucuronyl-spacer-doxorubicin prodrugs, such as HMR 1826, is important for the design of clin. studies, as well as for the development of more selective drugs. Enzyme histochem., immunohistochem., and the terminal deoxytransferase technique were applied using human cryopreserved cancer tissues, normal human, monkey, and mouse tissues, and human tumor xenografts to examine mechanisms underlying the selectivity of successful PMT with HMR 1826. It could unambiguously be shown by enzyme histochem. that necrotic areas in human cancers are the sites in which lysosomal .beta.-glucuronidase is liberated extracellularly in high local concns. The cells responsible for the liberation of the enzyme are mainly acute and chronic inflammatory cells, as shown by IHC. Furthermore, it could be demonstrated that .beta.-glucuronidase liberated in necrotic areas of tumors can activate HMR 1826, resulting in increased doxorubicin deposition in human tumor xenografts or in human lung cancers subjected to extracorporeal perfusion, compared to chemotherapy with doxorubicin. Addnl., the doxorubicin load to normal tissues was significantly reduced compared to chemotherapy with doxorubicin. Surprisingly, the increased doxorubicin deposition in tumors also resulted in strong antitumor effects also in cancers resistant to max. tolerated doses of systemic doxorubicin. Finally, toxicity studies in mice and monkeys revealed an excellent tolerability of HMR 1826, up to a dose of 3 g/m2 (monkeys). These data suggest that HMR 1826 is a promising candidate for clin. development.
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN **1999:441142** CAPLUS
DN 131:214493
TI Application of the ADEPT strategy to the MDR resistance in cancer chemotherapy
AU Desbene, Stephanie; Van, Hanh Dufat-Trinh; Michel, Sylvie; Tillequin, Francois; Koch, Michel; Schmidt, Frederic; Florent, Jean-Claude; Monneret, Claude; Straub, Rainer; Czech, Jorg; Gerken, Manfred; Bosslet, Klaus
CS Laboratoire de Pharmacognosie, URA CNRS 1310, Universite Paris V, Paris, F-75005, Fr.
SO Anti-Cancer Drug Design (1999), 14(2), 93-106
CODEN: ACDDEA; ISSN: 0266-9536
PB Oxford University Press
DT Journal
LA English
AB New prodrugs consisting of a .beta.-D-glucuronic acid linked to a multidrug resistance (MDR) reversal agent (verapamil, quinine or dipyridamole) through a self-immolative spacer were synthesized. Four of them were selected for their reduced cytotoxicity and .beta.-glucuronidase enzymic efficient hydrolysis. Combined use of these prodrugs with a .beta.-D-glucuronyl-spacer-doxorubicin (HMR 1826) according to an ADEPT strategy restored in vitro the sensibility of a MDR resistant strain.
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT